REMARKS

Reconsideration and allowance are respectfully requested.

Claims 71-134 are pending. Rejoinder of withdrawn claims 71-89, 110-131 and 134 is requested upon allowance of an elected product claim.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the attention of the Examiner related subject matter in Serial Nos. 09/738,879, 09/950,003, 10/240,606, 10/274,706, 10/484,883, 10/496,037, 10/518,229, 10/518,303, 10/582,687, 10/868,359, 10/902,285, 11/030,156, 11/440,749, 12/120,167 and 12/198,426. The Examiner is invited to consider their prosecution histories and the prior art of record in those applications, which are accessible through the PTO's Image File Wrapper (IFW), in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if she prefers.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hind-

sight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 90-93 and 108-109 were rejected under Section 103(a) as allegedly unpatentable over Leali (J. Biol. Chem. 276:37900-37908, 2001) in view of Casu (WO 98/42754) and Guo et al. (US 6,388,060). Applicants traverse because the extremely high sulfation degree (also referred to as a high sulfate/carboxyl ratio) of the claimed epiK5-N,O-oversulfate-derivatives and the absence of anticoagulant activity of these glycosaminoglycans would not have been attainable with a reasonable expectation of success when their invention was made. By a previously unrecognized improvement in the process for its production, Applicants opened a new approach to antithrombotic and antiviral therapies using very safe and effective therapeutic agents.

Applicants' present claims are directed to a new epiK5-N,O-oversulfate-derivative having a sulfation degree higher than 4, would not have been attainable with a reasonable expectation of success when their invention was made. In particular, the oversulfated heparin-like glycosaminoglycan is surprisingly devoid of anticoagulant activity. The Examiner is required to consider whether this improvement is more than the predictable use of prior art elements according to their established functions. See *KSR* at 1396.

Leali disclosed an N,O-sulfated polysaccharide having a sulfation degree of 3.84, but failed to teach or make obvious how to prepare epimerized, N,O-sulfated polysaccharides having a sulfation degree higher than 4. It would not have been obvious for one of ordinary skill in the art to prepare such angiostatic products substantially devoid of anticoagulant activity by oversulfation of an epimerized, N-sulfated polysaccharide

because the proposed invitation to experiment would not have had a reasonable expectation of success as shown by Casu (see discussion below).

Casu disclosed glycosaminoglycans having high antithrombotic activity in vitro, including epimerized and non-epimerized N,O-sulfated K5 polysaccharides having a sulfation degree of from 2 to 3.5. Their antithrombotic activity in vitro being assessed by determining especially the Anti-Xa but also the Anti-IIa activity (i.e., enzymatic activities in the coagulation cascade), and their activity in the activated Partial Thrombin Time (aPTT) test. The cited documents, however, neither teach nor make obvious how to prepare epimerized, N,O-sulfated polysaccharides having a sulfation degree higher than 4, which is devoid of anticoagulant activity (i.e., devoid of Anti-Xa, Anti-IIa and aPTT activities), with a reasonable expectation of success.

Applicants summarize Casu's process as follows. The glycosaminoglycans, each called "substrate" (see page 4, lines 4-11) used by Casu are heparin, heparan sulfate, and epimerized or non-epimerized K5 polysaccharide. The cited disclosure, however, is very confused and, as far as K5 polysaccharide derivatives are concerned, the process is not reproducible from Casu's disclosure. For example, epimerized K5 polysaccharide as prepared by Casu's process was and still is an unknown product. Further, epimerized and non-epimerized K5 polysaccharide are N-acetylated glycosaminoglycans.

Although Casu proposed that "biotechnological" supersulfated heparan sulfates and heparins, epimerized or not epimerized, obtained from the N-sulfated K5 polysaccharide may be used as starting material, there was absolutely no indication of its preparation given in the cited document or that it was actually present at any time.

Preparation of highly antithrombotic glycosaminoglycans occurred as follows.
(a) Preparation of oversulfated substrate by passage of the substrate through a cationic resin, treatment of a solution containing the substrate in acidic form with tetrabutylammonium hydroxide to pH 9, and isolation of tetrabutylammonium salt of the substrate by lyophilization and oversulfation. The obtained oversulfated substrate was completely N-desulfated (A-NH_2, see page 10, lines 22-23).
(b) Preparation of pyridine salt of the oversulfated substrate. The obtained salt was also completely N-desulfated.

(c) Desulfation of pyridine salt of the oversulfated substrate. The obtained partially O-desulfated product was completely N-desulfated. Its characteristics are reported in Table 3, wherein a very low percent of O-sulfate groups is reported (including the few data related to products derived from epimerized or non-epimerized K5 polysaccharide).
(d) N-resulfation of the partially desulfated products obtained. The obtained products are N-sulfated derivatives of the partially O-desulfated products of (c). Their characteristics are given in Table 4. They show that the sulfate/carboxyl ratio does not exceed 2.3 and the anticoagulant/antithrombotic parameters (where reported) are significant.
(e) Casu also disclosed an optional 6-O-resulfation of the N-resulfated product. But no product obtained by the 6-O-resulfation was described. In any case, the 6-O-resulfation would involve a loss of N-sulfate groups (see the following paragraph).

The obtained glycosaminoglycans, having a sulfate/carboxyl ratio from 2 to 3.5, possess high antithrombotic activity on the coagulation cascade parameters in vitro (see Table 4 in Casu). In this regard, Casu's process and products, notwithstanding their significant anticoagulant/antithrombotic parameter values, were not satisfactory for development of anticoagulant/antithrombotic heparin-like glycosaminoglycans. Applicants subsequently discovered the correct reaction conditions that result in the desired anticoagulant/antithrombotic heparin-like glycosaminoglycans having very good activity in all of the coagulation parameters (see Oreste et al., US 2002/0062019 and US 2009/0105192). They further improved the process for preparation using only the oversulfation conditions taught in the present specification and obtained a low-molecular-weight-heparin-like glycosaminoglycan derived from N-sulfated, epimerized and depolymerized K5 polysaccharide having qualitative biochemical parameters similar to those of low molecular weight heparin (see Oreste et al., US 2007/0155694).

US 2002/0062019 teaches that Casu's process has the drawback of incomplete 6-O or N-sulfation (see paragraph [0012]). More particularly, Casu taught:
- oversulfated low molecular weight heparin (ssLMWH) has a good Anti-Xa activity;
- the products of Examples 1-2 and 6 have an Anti-Xa activity even higher than that of ssLMWH (see Table 1); and

- the product of Example 16 (derived from eK5-PS) has Anti-Xa activity, a non-negligible aPTT activity, and a very high Anti-IIa activity (see Table 4). Thus, when Applicants' made their invention, Casu actually taught away from trying different N,O oversulfated glycosaminoglycans derived from epimerized K5-N-sulfate for use as pharmaceuticals for treating diseases other than those in the cardiovascular/hemobiological field. Applicants agree with Casu's teaching that the starting epimerized, N-sulfated K5 polysaccharide is structurally similar to heparan sulfate.

The Office Action contends that Guo disclosed processes for preparing highly sulfated uronic acid containing polysaccharide and that heparinoids having a degree of sulfation can be obtained using the processes. At column 3, lines 20-22, the cited document recited, "Quite surprisingly, the resulting heparinoids have a high degree of sulfation, up to 4 sulfates per disaccharide." Thus, a maximal limit of sulfation is given, but the cited document fails to make obvious how to prepare N,O-oversulfated, epimerized K5 polysaccharide having a sulfation degree higher than 4.

Applicants observe that Guo attained the maximal degree of sulfation (4.01 and 4.07, similar to four sulfates per disaccharide) by using heparin as a starting material that already contains sulfate groups having a degree of sulfation of about 2. Thus, the starting heparin (which, well-known, is partially N-acetylated) already contained, beside N-sulfo groups, O-sulfo groups in position 6 of glucosamine, O-sulfo groups in position 2 of uronic units, and a low percent of glucosamine 3-0-sulfate groups. Using heparan sulfate, which was taught by Casu and emphasized in the Office Action as structurally similar to N-sulfated, epimerized K5 polysaccharide, Guo obtained an oversulfated product having a sulfation degree of 2.57.

The cited documents do not teach or make obvious any process allowing the preparation of N,O-oversulfated heparan sulfate or epimerized, N-sulfated K5 polysaccharide having a sulfation degree higher than 4. By contrast, Applicants invented a new method (claim 71, withdrawn with traverse) which, by an improvement in the preparation of the tertiary amine or quaternary ammonium salt of the starting epimerized, N-sulfated K5 polysaccharide, allows the attainment of sulfation degrees higher than 4 after final N-sulfation.

The Office Action alleged, "It would have been obvious to one skilled in the art at the time the invention was made to prepare epimerized products having a degree of sulfation up to 4." Applicants respectfully draw the Examiner's attention to the fact that epimerized N-sulfated K5 polysaccharide is structurally similar to heparan sulfate and, hence, according to Guo's teachings, at the time Applicants' invention was made, a sulfation degree of only about 2.57 would have been predicted with a reasonable expectation of success.

Applicants also draw the Examiner's attention to the fact that it would not have been obvious to one of ordinary skill in the art to prepare epimerized products having a degree of sulfation up to 4 for uses other than those in the cardiovascular field starting from epimerized K5-N-sulfate because Casu teaches away from doing so (see above).

The Office Action also alleged, "Casu teaches that the epimerized and non-epimerized products can be used interchangeably. Thus, the skilled artisan would expect the epimerized and non-epimerized products to have similar activity." Applicants respectfully disagree because the second sentence in this quote was made with hindsight. Casu actually suggested that it would have been expected that epimerized and non-epimerized products have similar antithrombotic (i.e., similar Anti-Xa, Anti-IIa and aPTT) activities (see, in particular Table 4). Without the teaching of the present specification, one of ordinary skill in the art would not have had a reasonable expectation of success to obtain a product having Anti-Xa, Anti-IIa and/or aPTT activities by oversulfation of epimerized K5-N-sulfate.

This interpretation is supported by the structure of the present, starting epiK5-N-sulfate derivatives that contain 20%-60% iduronic acid, similar to heparan sulfate. Thus, one of ordinary skill in the art would have expected that its oversulfation followed by N-sulfation results in a product having a structure similar to oversulfated heparin or low molecular weight heparin (both containing 70% iduronic acid). In accordance with Casu, the expected product would be predicted to have a very high Anti-Xa activity and also an anticoagulant activity, even though lower than that of (very high) heparin.

The starting epimerized, N-sulfated K5 polysaccharide is structurally similar to heparan sulfate. Hence, Guo would have suggested that a sulfation degree of about

2.57 would be obtained. By Applicants' process, however, they succeeded in preparing an N,O-oversulfated product having a sulfation degree higher than 4 and devoid of anti-coagulant (i.e., Anti-Xa, Anti-IIa and aPTT) activities. This result, contrary to the assertions made in the Office Action, would not have been obvious and was also extremely surprising because oversulfation of an epiK5-N-sulfate-derivative resulted in a product similar to an oversulfated heparin, which Casu taught should have extremely high Anti-Xa activity.

Applicants' results were also unexpected because the claimed product shows other desirable activities, but certainly not significant Anti-Xa, Anti-IIa or aPTT activity.

Further, the Office Action alleged, "Leali teaches the desirability of heparin-mimiking structures." But those products, which lack iduronic units, do not have heparin-like structures. Also, as taught by Casu, oversulfated heparin possesses anticoagulant and very high antithrombotic activities: These properties of a heparin-like oversulfated glycosaminoglycan are undesirable, and a big drawback for uses other than those in the cardiovascular field.

The claimed epiK5-N,O-oversulfate-derivatives are true oversulfated heparin-like glycosaminoglycans that are unexpectedly devoid of anticoagulant/antithrombotic activity while retaining other non-anticoagulant-type activities (including, but not limited to, angiostatic, antiviral, and anti-inflammatory activities). They are rendered even more attractive by their very great anionic power due to their high sulfation degree, even higher than that only attained with heparin before Applicants' invention was made.

The Office Action also alleged, "Leali teaches that a high degree of sulfation is important for activity, and teaches a product having a degree of sulfation of 3.84, which is very close to 4." Applicants respectfully dissent from this allegation, which appears to have been made with hindsight, because at the time their invention was made, although Leali disclosed that the sulfation degree is important for the activity, the prior art did not teach how to attain a sulfation degree higher than 4 in an epiK5-N,O-sulfate with a reasonable expectation of success. The non-epimerized K5-N,O-oversulfate (which is 100% N-sulfated) has a sulfation degree of 3.84, which is close to the sulfation degree

of 3.55 of the intermediate epiK5-amine-O-oversulfate (which is 0% N-sulfated) that is described in Example 4(b) of Applicants' specification.

Applicants found that preparing a tertiary amine or quaternary ammonium salt of epiK5-N-sulfate by simply maintaining the solution containing said salt at pH 7 for 30-60 minutes (i.e., an apparently small modification of the process disclosed by Leali), a very highly sulfated epiK5-amine-O-oversulfate is obtained and, surprisingly, its N-sulfation provides a new epiK5-N,O-oversulfate having a high degree of sulfation, even higher than that previously attained by oversulfation of heparin only. Why "surprisingly"? Because one of ordinary skill in the art also would have known that the maximal degree of sulfation of a N-deacetylated, N,O-sulfated K5 polysaccharide, epimerized or not epimerized, is 5 (one sulfate group for each hydroxyl per disaccharide unit). A sulfation degree of 4.35 (see the product of Example 4) means that in a large portion of disaccharide units of chains forming the epiK5-N,O-oversulfate-derivative, all five possible sites are sulfated. Thus, Applicants' small modification in process conditions results in an unexpectedly large difference in results.

One of ordinary skill in the art also would have known that the molecular mass of the sulfate group is 80 and that it would not have been obvious to foresee the presence of more than four heavy groups per disaccharide unit in a K5-N,O-sulfate, epimerized or not epimerized, considering the steric hindrance therebetween.

Moreover, Applicants were surprised by their finding and tentatively hypothesize, a posteriori, that keeping the solution containing tertiary amine or quaternary ammonium salt at pH 7 for a certain time period allowed "complete" formation of the salt and better availability of sites to be sulfated. This hypothesis, which has not been verified, was not foreseeable in the prior art. In any case, patentability is not negatived by the manner in which the invention was made and may also derive from a discovery.

Finally, the attached Rule 132 declaration by one of the inventors (Oreste) shows the results of a comparative experiment ("Declaration") wherein oversulfation is carried out under strong conditions on an epiK5-N-sulfate tetrabutylammonium salt and isolated under reaction conditions of the present invention (pH 7 maintained for one hour, then isolation), Leali (pH 7 and immediate isolation), or Casu (pH 9 and immediate isolation).

In the Declaration, sulfation profiles of the obtained epiK5-mine-O-oversulfates are compared to each other and with non-epimerized K5-amine-O-oversulfate prepared by the process described in the present specification (pH 7 maintained for one hour, then isolation). This comparison establishes that the sulfation profile of epiK5-amine-O-oversulfate products prepared under the reaction conditions described by Leali and Casu are different from products prepared under the reaction conditions described in the present specification. For example, glucosamine 3-O-sulfate content is 70%. Also shown is that oversulfation of a non-epimerized K5-N-sulfate according to the present specification provides K5-amine O-oversulfate having a sulfation degree of 2.79 (cf. Leali's sulfation degree of 3.84 after N-sulfation) and a glucosamine 3-O-sulfate content lower than 40%.

Thus, Oreste's Declaration demonstrates that a characteristic of the claimed epiK5-N,O-oversulfate is its high glucosamine 3-O-sulfate content (at least 40%, as it appears in claim 95), which can be easily obtained under the conditions described in the present specification. Moreover, such a high glucosamine 3-O-sulfate content cannot be attained, even under the strong oversulfation conditions of the Declaration, by using Leali's and Casu's processes or even under the reaction conditions of the present specification starting from a non-epimerized K5- N-sulfate.

The above arguments and results shown in the Declaration prove the claimed epiK5-N,O-oversulfate-derivatives are not obvious, as well as the close relationship between the process according to present claims 70-89 and the products of present claims 90-109. Therefore, the present claims are patentable over Leali, Casu and Guo.

Claims 132-133 were rejected under Section 103(a) as allegedly unpatentable over Leali in view of Casu and Guo as previously applied, and further in view of Doshi (US 5,798,356). Applicants traverse because their above arguments also apply with the same persuasiveness as to the nonobviousness of claims 132-133.

If a modification proposed by the Examiner would render a prior art invention inoperable for its intended purpose, then the cited prior art effectively teaches away from the proposed modification and fails to establish a prima facie case of obviousness. See *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984). Moreover, if the proposed modifi-

cation would change the principle of operation of the prior art invention being modified, then the cited prior art also fails to establish a prima facie case of obviousness. See *In re Ratti*, 123 USPQ 349 (CCPA 1959).

Here, Casu teaches against including an oversulfated heparin-like glycosaminoglycan in a pharmaceutical composition for angiostatic treatment because its predicted activity on coagulation parameters in a treated patient would have been a severe drawback to performance of that treatment, as well as any treatment other than that in the cardiovascular and, more specifically, a hemobiological field. For this reason, Doshi's disclosure of an angiostatic synthetic product (which is active in treatment of vascular diseases, including thrombosis, see column 7, lines 19-20) cannot be relied upon in the context of the four cited documents to establish a case of prima facie obviousness for a non-antithrombotic heparin-like glycosaminoglycan according to claims 132-133.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

Gary R. Tanigawa
Reg. No. 43,180

901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100